Abstract Type : Oral Presentation
Abstract Submission No. : F-007778

Applying Integrative Multi-omic Profiling in Two Human Decedents Receiving Pig Heart Xenografts Reveals Early Immune-Cell Responses Indicative of Perioperative Cardiac Xenograft Dysfunction.

Brendan Keating[1], Robert Montgomery[2], Eloi Schmauch[3], Brian Piening[4], Michael Snyder[5]

[1]Department of Surgery, University of Pennsylvania, USA
[2]Department of Surgery, New York University, USA
[3]Department of Computer Science and Artificial Intelligence, Broad Institute of MIT and Harvard,, USA
[4]Department of Genetics, Providence Cancer Center, Portland, USA
[5]Department of Genetics, Stanford University, USA

Introduction: Recent advances in xenotransplantation in living and decedent humans using pig heart xenografts have laid promising groundwork towards future emergency use and first-in-human trials. Major obstacles remain however, including a lack of knowledge of the genetic incompatibilities between pig donors and human recipients, which may lead to harmful immune responses against the xenograft and/or physiological dysfunction. In 2022, two gene-edited pig heart xenografts were transplanted into two brain-dead human decedents, primarily to evaluate onset of hyper-acute antibody mediated rejection and sustained xenograft function over 3-days.

Methods: We performed multi-omic profiling to assess the dynamic interactions between two pig heart-xenografts transplanted into two human decedents. We generated transcriptomic, lipidomic, proteomic and metabolomics datasets, across blood samples every 6 hours, as well as histological and transcriptomic tissue profiling, over the 3-day procedures to biological changes that correlate with immune-related outcomes and xenograft function.

Results: In decedent 1 we observed early immune-activation changes in PBMCs (using single-cell RNA-seq) and xenograft tissue (using single-nuclei RNA-seq and spatial transcriptomics) leading to profound downstream T cell and NK cell activity, which collectively represented over 20% of all blood cells in the final 3 day procedure timepoints. Longitudinal multi-omic integrative analyses from blood and tissue, indicates ischemia reperfusion injury (IRI) in decedent 1, which is exacerbated by minimal immunosuppression of T cells, is consistent with perioperative cardiac xenograft dysfunction transcriptome signatures. We also observe significant cellular metabolism and liver damage pathway changes after 42 hours in decedent 1 that correlates with organ-wide physiological dysfunction. Decedent 2 had normal xenograft functioning with relatively minor changes across the multiomic profiling datasets.

Conclusion: Single-cell and multi omics approaches reveal fundamental insights into early molecular and immune responses indicative of IRI and PCXD in a human decedent model recieving gene-modified pig heart xenografts, that were not evident in the initial clinical findings.